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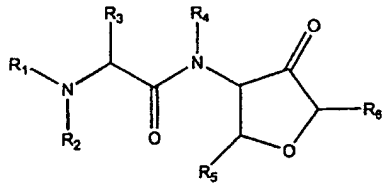
(54) Title: FURANONE DERIVATIVES AS INHIBITORS OF CATHEPSIN S



(II)

(57) Abstract

Cathepsin S is a highly active cysteine protease belonging to the papain superfamily. It is found mainly in lymph nodes, spleen, and macrophages and this limited occurrence suggests the potential involvement of this enzyme in the pathogenesis of degenerative disease. The invention relates to novel protease inhibitors, particularly inhibitors of the cysteine proteases of the papain superfamily and more particularly to Cathepsin S. The inhibitors are Furanone derivatives of Formula (II) which have a characteristic non–hydrogen substituent R5. They are selective over other members of the family and in particular show selectivity over other members of the Cathepsin family such as L and K.

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Furanone Derivatives as Inhibitors of Cathepsin S

Field of the invention.

Cathepsin S is a highly active cysteine protease belonging to the papain superfamily. Its primary structure is 57%, 41% and 45% homologous with that of the human cathepsin L and H and plant cysteine proteases papain respectively, although only 31% homologous with Cathepsin B.

It is found mainly in lymph nodes, spleen, and macrophages and this limited occurrence suggests the potential involvement of this enzyme in the pathogenesis of degenerative disease.

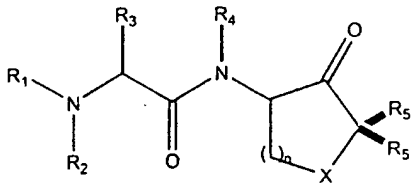
Moreover, it has been found that destruction of Ii by proteolysis is required for MHC class II molecules to bind antigenic peptides, and for transport of the resulting complex to the cell surface. Furthermore, it has been found that Cathepsin S is essential in B cells for effective Ii proteolysis necessary to render class II molecules competent for binding peptides. Therefore, the inhibition of this enzyme may be useful in modulating class II-restricting immune response (WO 97/40066).

Selective inhibition of a single protease in a complex mixture of proteolytic enzymes and more especially over other members of the same enzyme class or family is imperative as incorrect regulation of proteolytic activity can lead to unwanted pathological conditions such as hypertension, blood clotting or worse. This has lead to the search for inhibitors that selectively inhibit only one member of a proteolytic family, a problem that is very relevant to the Cathepsin family, which have a high degree of homology.

The invention relates to novel protease inhibitors, particularly inhibitors of the cysteine proteases of the papain superfamily and more particularly to Cathepsin S. The inhibitors of the invention are selective over other members of the family and in particular show selectivity over other members of the Cathepsin family such as L and K.

Description of the related art.

In WO 97/40066, the use of inhibitors against Cathepsin S is described. The inhibition of this enzyme is suggested to prevent or treat disease caused by protease activity. WO 98/50533 describes the use of compounds according to the formula (I).



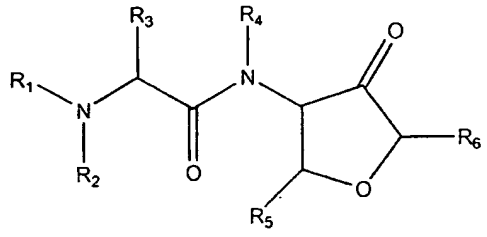
(I)

It is suggested the compounds of this formula, known as the tetrahydrofuran-3-ones, are useful as inhibitors to proteases, in particular the papain superfamily; specifically those of the Cathepsin family; and particularly Cathepsin K.

Summary of the invention

The present invention provides compounds which inhibit the cysteine protease Cathepsin S but do not significantly inhibit other members of the papain superfamily. The compounds of the present invention are useful for the treatment of diseases caused by or enhanced by the presence or the activity of the protease enzyme.

Accordingly, the first aspect of the invention provides a compound according to formula (II):

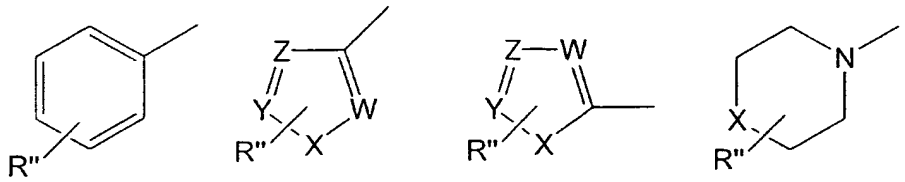


(II)

wherein:

R1 = R' , R'C(O) , R' C(S), R' SO2 , R' OC(O), R' NHC(O)

R' =



X, = O, S, NH, W, Y, Z = CH, N;

R'' = single or multiple ring substitution combinations taken from:

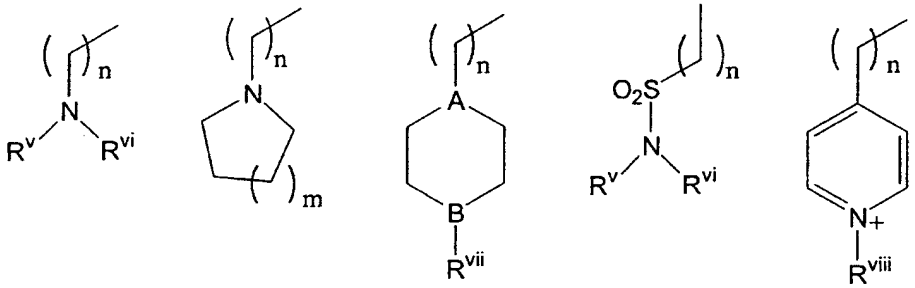
H, C1-7-alkyl, C3-6-cycloalkyl, OH, SH, Amine, Halogen;

R2, R4 = H, C1-7-alkyl, C3-7-cycloalkyl;

R3 = C1-7-alkyl, C3-7-cycloalkyl, Ar- C1-7-alkyl;

R5 = C1-7-alkyl, Halogen, Ar- C1-7-alkyl, C1-3-alkyl-CONR''', R^{iv};

R^{iv} =



where n = 1-3, m = 1-3;

R^{v}, R^{vi} = H, C1-7-alkyl;

A = N, CH;

B = N, O, S, CH;

R^{vii} = absent when B = O, S; or R^{vii} = H, C1-7-alkyl when B = N, CH;

R^{viii} = O, C1-7-alkyl;

R6 = H, C1-7-alkyl, Ar- C1-7-alkyl, C1-3-alkyl-SO2-R^{ix},

C1-3-alkyl-C(O)-NHR^{ix} or CH_2XAr, where X and Ar are as defined herein;

and pharmaceutically acceptable salts thereof.

'C1-7-alkyl' as applied herein is meant to include straight and branched chain aliphatic carbon chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof. Additionally, any C1-

7-alkyl may optionally be substituted by one or two halogens and/or a heteroatom S, O, NH. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or 2 hydrogen atoms.

'C1-3-alkyl' as applied herein includes methyl, ethyl, propyl, isopropyl, cyclopropyl, any of which may be optionally substituted as described in the paragraph above.

'Amine' includes NH2, NHC1-3-alkyl or N(C1-3-alkyl)2.

'Halogen' as applied herein is meant to include F, Cl, Br, I, particularly chloro and preferably fluoro.

'C3-6-cycloalkyl' as applied herein is meant to include any variation of 'C1-7-alkyl' which additionally contains a C3-6 carbocyclic ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

'Ar- C1-7-alkyl' as applied herein is meant to include a phenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl or thienyl aromatic ring (Ar) attached through a 'C1-7-alkyl' (defined above) to the dihydro-(3H)-furanone ring system or in the case of R3 linked directly to the molecule backbone. Optionally, the aromatic ring Ar may be substituted with halogen, C1-3-alkyl, OH, OC1-3-alkyl, SH, SC1-3-alkyl, amine and the like.

'C1-3-alkyl-CONR''', R^{iv}' as applied herein is meant to include straight or branched carbon chain substituted with a 1°, 2° or 3° carboxamide wherein R''', R^{iv} includes H and Me.

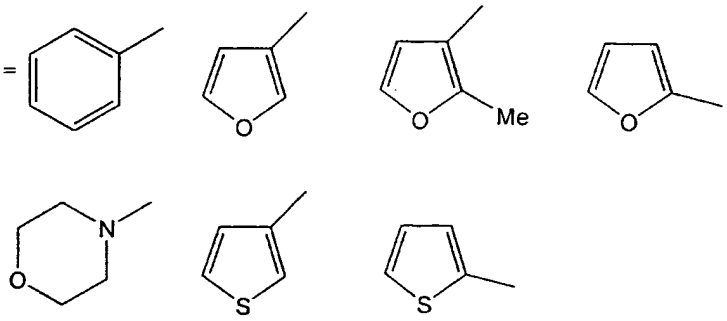
'C1-3-alkyl-SO_2-R^{ix}, as applied herein is meant to include straight or branched carbon chain substituted with a sulphone wherein R^{ix} includes 'C1-7-alkyl', 'Ar- C1-7-alkyl', 'C3-6-cycloalkyl'.

'C1-3-alkyl-C(O)-NHR^{ix}, as applied herein is meant to include straight or branched carbon chain substituted with a secondary carboxamide wherein R^{ix} includes 'C1-7-alkyl', 'Ar- C1-7-alkyl', 'C3-6-cycloalkyl'.

If a chiral centre is present, all isomeric forms are intended to be covered.

Suitably compounds of the present invention have

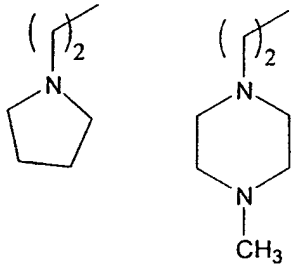
R1 = R'C(O)

Where R' = 

R2 and R4 = H;

R3 = n-butyl, t-butyl, 3-(2,2-dimethylpropyl), 4-(2-methylbutyl), 4-(3,3-dimethylbutyl), 4-(3,3-dimethyl-2-methylbutyl), 4-(3-methyl-2-methylbutyl), 5-(2-methyl-3-methylpentyl);

R5 = CH_3, C_2H_5, CH_2Ar, CH_2CONH_2, $(CH_2)_2CONH_2$,



R6 = H, CH_2-X-Ar, where X and Ar are as defined above

or permutations thereof.

Both (R) and (S) stereochemistries at the furan 5-position are encompassed by the invention with (S) being preferred in some cases, for instance when R5 = CH_3;

A further aspect of the invention comprises a method employing the compounds of formula II for the treatment of diseases wherein cathepsin S is a factor, ie diseases or conditions alleviated or modified by inhbition of cathepsin S, preferably without substantial concomitant inhbition of other members of the papain superfamily. Examples of such diseases or conditions include those enumerated in WO 97/40066, such as autoimmune diseases, allergies, multiple sclerosis, rheumatoid arthritis and the like. the invention further provides the use of the compounds of formula II in therapy and in the manufacture of a medicament for the treatment of diseases or conditions alleviated or moderated by inhibition of cathepsin S.

The compounds of the invention can form salts which form an additional aspect of the invention. Appropriate pharmaceutically acceptable salts of the compounds of Formula II include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, isethionate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-napthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids. The compounds of Formula II may in some cases be isolated as the hydrate.

While it is possible for the active agent to be administered alone, it is preferable to present it as part of a pharmaceutical formulation. Such a formulation will comprise the above defined active agent together with one or more acceptable carriers/excipients

and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an orally administered formulation. The formulations may conveniently be presented in unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of Formula I or its pharmaceutically acceptable salt in conjunction or association with a pharmaceutically acceptable carrier or vehicle. If the manufacture of pharmaceutical formulations involves intimate mixing of pharmaceutical excipients and the active ingredient in salt form, then it is often preferred to use excipients which are non-basic in nature, i.e. either acidic or neutral.

Formulations for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion and as a bolus etc.

With regard to compositions for oral administration (e.g. tablets and capsules), the term suitable carrier includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone

(Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

The term "N-protecting group" or "N-protected" and the like as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl,

trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl gropus such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include formyl, acetyl, allyl, F-moc, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz).

Hydroxy and/or carboxy protecting groups are also extensively reviewed in Greene ibid and include ethers such as methyl, substituted methyl ethers such as methoxymethyl, methylthiomethyl, benzyloxymethyl, t-butoxymethyl, 2-methoxyethoxymethyl and the like, silyl ethers such as trimethylsilyl (TMS), t-butyldimethylsilyl (TBDMS) tribenzylsilyl, triphenylsilyl, t-butyldiphenylsilyl triisopropyl silyl and the like, substituted ethyl ethers such as 1-ethoxymethyl, 1-methyl-1-methoxyethyl, t-butyl, allyl, benzyl, p-methoxybenzyl, dipehenylmethyl, triphenylmethyl and the like, aralkyl groups such as trityl, and pixyl (9-hydroxy-9-phenylxanthene derivatives, especially the chloride). Ester hydroxy protecting groups include esters such as formate, benzylformate, chloroacetate, methoxyacetate, phenoxyacetate, pivaloate, adamantoate, mesitoate, benzoate and the like. Carbonate hydroxy protecting groups include methyl vinyl, allyl, cinnamyl, benzyl and the like.

Compounds are synthesised by a combination of chemistries, performed either in solution or on the solid phase. The general scheme for preparation of the furanone ring system is given in scheme 1, commencing from either a commercially available chiral aminoacid derivative or a stereoselectively prepared aminoacid, for instance from Scheme 2.

The stereoselective synthesis detailed in Scheme 2 was adapted from Blaskovich, M.A., Evinder, G., Rose, N. G. W., Wilkinson, S., Luo, Y. and Lajoie, G. A. *J. Org. Chem*, 63, 3631-3646, 1998. The addition of Grignard reagent to compound **(10)** yielding the (R) isomer of compound **(11)** is applicable to a huge range of alternative Grignard reagents. This allows ready access to analogues of compound **(15)** by standard Grignard chemistry to produce R5 analogues embraced by formula (II). The R5 substituent confers many beneficial qualities to molecules of general formula (II) including improvements in potency, selectivity and offers the potential to append inhibitor molecules with a basic functionality to improve solubility and pharmacokinetic properties. Additionally, molecules of formula (II) where R5 is alkyl and not simply hydrogen show good chiral stability at the furanone alpha carbon (ring position 4).

Note particularly the presence of the substituent R5 in formula (II) in comparison with the absence of any substituent in the same position in formula (I) according to WO 98/50533.

An alternative route towards chiral β-alkyl serine aminoacids is detailed in scheme 3, commencing from D-mannitol. The addition of organocuprate reagents to the advanced oxirane intermediate **(44)** is applicable to a wide selection of reagents, giving ready access to analogues of compound **(15)** ie analogues of R5 in formula (II).

To access molecules containing potential binding elements in R6 formula (II), a number of synthetic chemistry routes are available. One example extends the basic concepts developed for the preparation of the furanone ring system depicted in

schemes 1 and 8 (scheme 4). Intermediate **(51),** which can be prepared with alternative ring stereochemistries from alternative threonine isomers, provides access to the functionalities defined in R6 formula (II).

An alternative route to access molecules containing potential binding elements in R6 from formula (II), is based upon transformation of a chiral sugar starting material (scheme 5). Intermediate **(59),** which can be prepared with alternative ring stereochemistries from alternative starting sugar isomers using conventional saccharide chemistry, provides access to many functionalities in R6 formula (II).

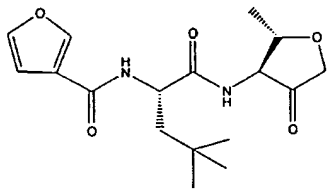
Many active inhibitors contain commercially available amino acid residues such as L-leucine, L-norleucine etc (see table 1). Alternatively, active inhibitors contain new and novel hydrophobic amino acids, which are prepared following the chemistry detailed in scheme 6. The synthesis detailed in Scheme 6 was adapted from Dexter, C. S. and Jackson, R. F. W. *Chem.Commun.* 1, 75-76, 1998, and allows ready access to analogues embraced by R3 in formula (II). The side chains of some of the novel, multiply branched alpha-amino acid building blocks exemplified herein can be thought of as hybrids of the properties of combinations of other amino acid side chains, such as those of norleucine and t-butylalanine and are thus referred to as "hybrids" in the tables.

The furanone building blocks (synthesis exemplified in Scheme 1) are utilised in a solid phase synthesis of inhibitor molecules (typically 5-25mg product) detailed in Scheme 7. Alternatively, for larger scale syntheses, full preparation of inhibitors by solution phase chemistry may be performed as detailed in Scheme 8.

Compounds were previously named (for instance in the priority document GB 9911417.5) using amino acid nomenclature i.e. a sidechain of 2,2-dimethylpropyl was termed the aminoacid *tert*-butylalanine. The current specification contains novel aminoacids for which common names are not available. Therefore, all previously

exemplified and new compounds are re-named following IUPAC guidelines. For example, the compound below was previously named :-

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-*tert*-butyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone



Under the new naming regime, the compound will be termed as:-

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide.

Unless otherwise specified, where a chiral centre is present in a molecule but not assigned, both R and S isomers are intended.

Further compounds of the present invention include, but are not limited to, the following examples;

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylbutyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylbutyl}amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

Furan-3-carboxylic acid [4-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [4-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-methylpentyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4-methylpentyl}amide,

Furan-3-carboxylic acid [4-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylpentyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylpentyl}amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [3,3,4-trimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [3,3,4-trimethyl -1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3,4-trimethylpentyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]- 3,3,4-trimethylpentyl}amide,

Furan-3-carboxylic acid [3,3,4-trimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [3,4-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [3,4-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,4-dimethylpentyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,4-dimethylpentyl}amide,

Furan-3-carboxylic acid [3,4-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Furan-3-carboxylic acid [4,5-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)hexyl]amide,

Furan-3-carboxylic acid [4,5-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4,5-dimethylhexyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4,5-dimethylhexyl}amide,

Furan-3-carboxylic acid [4,5-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

Furan-3-carboxylic acid [3-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-3-phenylbutyl]amide,

Furan-3-carboxylic acid [3-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-methyl-3-phenylbutyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3-methyl-3-phenylbutyl}amide,

Furan-3-carboxylic acid [3-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-4-phenylbutyl]amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-4-phenylbutyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-4-phenylbutyl}amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-5-phenylpentyl]amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

Furan-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-5-phenylpentyl]amide,

Furan-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-5-phenylpentyl}amide,

Furan-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylbutyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylbutyl}amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

Thiophene-3-carboxylic acid [4-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [4-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-methylpentyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4-methylpentyl}amide,

Thiophene-3-carboxylic acid [4-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylpentyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylpentyl}amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [3,3,4-trimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [3,3,4-trimethyl -1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3,4-trimethylpentyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]- 3,3,4-trimethylpentyl}amide,

Thiophene-3-carboxylic acid [3,3,4-trimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [3,4-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [3,4-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,4-dimethylpentyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,4-dimethylpentyl}amide,

Thiophene-3-carboxylic acid [3,4-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Thiophene-3-carboxylic acid [4,5-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)hexyl]amide,

Thiophene-3-carboxylic acid [4,5-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4,5-dimethylhexyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4,5-dimethylhexyl}amide,

Thiophene-3-carboxylic acid [4,5-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

Thiophene-3-carboxylic acid [3-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-3-phenylbutyl]amide,

Thiophene-3-carboxylic acid [3-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-methyl-3-phenylbutyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3-methyl-3-phenylbutyl}amide,

Thiophene-3-carboxylic acid [3-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-4-phenylbutyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-4-phenylbutyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-4-phenylbutyl}amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-5-phenylpentyl]amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

Thiophene-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-5-phenylpentyl]amide,

Thiophene-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-5-phenylpentyl}amide,

Thiophene-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylbutyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylbutyl}amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

2-Methylfuran-3-carboxylic acid [4-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [4-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-methylpentyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4-methylpentyl}amide,

2-Methylfuran-3-carboxylic acid [4-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylpentyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylpentyl}amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [3,3,4-trimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [3,3,4-trimethyl -1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3,4-trimethylpentyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]- 3,3,4-trimethylpentyl}amide,

2-Methylfuran-3-carboxylic acid [3,3,4-trimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [3,4-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [3,4-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,4-dimethylpentyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,4-dimethylpentyl}amide,

2-Methylfuran-3-carboxylic acid [3,4-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

2-Methylfuran-3-carboxylic acid [4,5-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)hexyl]amide,

2-Methylfuran-3-carboxylic acid [4,5-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4,5-dimethylhexyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4,5-dimethylhexyl}amide,

2-Methylfuran-3-carboxylic acid [4,5-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

2-Methylfuran-3-carboxylic acid [3-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-3-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid [3-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-methyl-3-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3-methyl-3-phenylbutyl}amide,

2-Methylfuran-3-carboxylic acid [3-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-4-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-4-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-4-phenylbutyl}amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-5-phenylpentyl]amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

2-Methylfuran-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-5-phenylpentyl]amide,

2-Methylfuran-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-5-phenylpentyl}amide,

2-Methylfuran-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylbutyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

1*H*-Pyrrole-3-carboxylic acid [4-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [4-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-methylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4-methylpentyl}amide,

1*H*-Pyrrole-3-carboxylic acid [4-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylpentyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3,4-trimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3,4-trimethyl -1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3,4-trimethylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]- 3,3,4-trimethylpentyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3,3,4-trimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,4-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,4-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,4-dimethylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,4-dimethylpentyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3,4-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [4,5-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)hexyl]amide,

1*H*-Pyrrole-3-carboxylic acid [4,5-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4,5-dimethylhexyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4,5-dimethylhexyl}amide,

1*H*-Pyrrole-3-carboxylic acid [4,5-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-3-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-methyl-3-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3-methyl-3-phenylbutyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-4-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-4-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-4-phenylbutyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-5-phenylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-5-phenylpentyl]amide,

1*H*-Pyrrole-3-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-5-phenylpentyl}amide,

1*H*-Pyrrole-3-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

N-[3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]benzamide,

N-[3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)butyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylbutyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylbutyl}benzamide,

N-[3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)butyl]benzamide,

N-[4-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]benzamide,

N-[4-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-methylpentyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4-methylpentyl}benzamide,

N-[4-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]benzamide,

N-[3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylpentyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylpentyl}benzamide,

N-[3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[3,3,4-trimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]benzamide,

N-[3,3,4-trimethyl -1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3,4-trimethylpentyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]- 3,3,4-trimethylpentyl}benzamide,

N-[3,3,4-trimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[3,4-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]benzamide,

N-[3,4-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,4-dimethylpentyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,4-dimethylpentyl}benzamide,

N-[3,4-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]benzamide,

N-[4,5-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)hexyl]benzamide,

N-[4,5-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)hexyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4,5-dimethylhexyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4,5-dimethylhexyl}benzamide,

N-[4,5-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)hexyl]benzamide,

N-[3-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-3-phenylbutyl]benzamide,

N-[3-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-methyl-3-phenylbutyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3-methyl-3-phenylbutyl}benzamide,

N-[3-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]benzamide,

N-[3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-4-phenylbutyl]benzamide,

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N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-4-phenylbutyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-4-phenylbutyl}benzamide,

N-[3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]benzamide,

N-[3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-5-phenylpentyl]benzamide,

N-[3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]benzamide,

N-[1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-5-phenylpentyl]benzamide,

N-{1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-5-phenylpentyl}benzamide,

N-[3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]benzamide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylbutyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylbutyl}amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)butyl]amide,

Morpholine-4-carboxylic acid [4-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [4-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-methylpentyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4-methylpentyl}amide,

Morpholine-4-carboxylic acid [4-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

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Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethylpentyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethylpentyl}amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [3,3,4-trimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [3,3,4-trimethyl -1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3,4-trimethylpentyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]- 3,3,4-trimethylpentyl}amide,

Morpholine-4-carboxylic acid [3,3,4-trimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [3,4-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [3,4-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,4-dimethylpentyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,4-dimethylpentyl}amide,

Morpholine-4-carboxylic acid [3,4-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide,

Morpholine-4-carboxylic acid [4,5-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)hexyl]amide,

Morpholine-4-carboxylic acid [4,5-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4,5-dimethylhexyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-4,5-dimethylhexyl}amide,

Morpholine-4-carboxylic acid [4,5-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)hexyl]amide,

Morpholine-4-carboxylic acid [3-methyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-3-phenylbutyl]amide,

Morpholine-4-carboxylic acid [3-methyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3-methyl-3-phenylbutyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3-methyl-3-phenylbutyl}amide,

Morpholine-4-carboxylic acid [3-methyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-3-phenylbutyl]amide,

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Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-4-phenylbutyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-4-phenylbutyl}amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-4-phenylbutyl]amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-5-phenylpentyl]amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(2-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

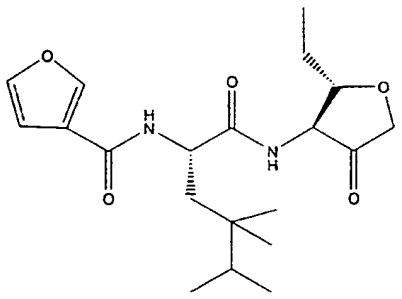
Morpholine-4-carboxylic acid [1S-(2-carbamoylmethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)-3,3-dimethyl-5-phenylpentyl]amide,

Morpholine-4-carboxylic acid {1S-[2-(2-dimethylaminoethyl)-4-oxo-tetrahydrofuran-3-ylcarbamoyl]-3,3-dimethyl-5-phenylpentyl}amide,

Morpholine-4-carboxylic acid [3,3-dimethyl-1S-(4-oxo-2-pyrrolidin-1-ylmethyl-tetrahydrofuran-3-ylcarbamoyl)-5-phenylpentyl]amide,

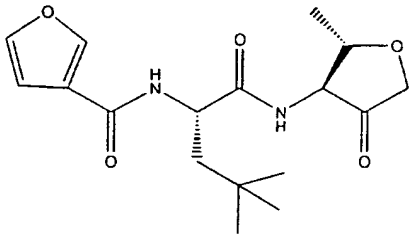
and pharmaceutically acceptable salts thereof.

Example molecules prepared using the general chemistries outlined above and by the methods detailed in the experimental are shown in Tables 1 and 2. Judicial combination of R1, R3 and R5 substituents in general formula (II) yields potent and selective inhibitors of cathepsin S e.g. Furan-3-carboxylic acid [3,3,4-trimethyl -1S-(2S-ethyl-4-oxo-tetrahydrofuran-3-ylcarbamoyl)pentyl]amide:



Ki mammalian cath S (15nM), murine cath S (149nM) rat cath S (271nM), cathepsin L (> 100μM), cathepsin K (5.5μM). Molecules may be chosen which show a range of activities for mammalian, murine and rat cathepsin S (see Table 2) which may exemplify many facets of an inhibitor development programme e.g. activities in murine or mammalian cell-based assays, dosing of species for disease-related animal models etc.

Molecules of general formula (II) have the potential for good oral bioavailability e.g.



Furan-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide dosed i.v. and orally at 10mg / kg to mice gave an oral bioavailability of *% (F)* 58.

Experimental Section

Solution Phase Chemistry

Example 1. Furan-3-carboxylic acid [3,3-dimethyl-1S-(2S-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)butyl]amide **(4)**

Following general chemistry scheme 8

(a) General method for the synthesis of N-Boc protected diazoketones, exemplified by (2S, 3S)-N-Boc-O-t-butyl-L-threonyldiazomethane **(1)**

(2S, 3S)- N-Boc-O-t-butyl-L-threonine (1.2g, 4.2mmol) was dissolved in dry DCM (20mL) and N-methylmorpholine (1mL, 2.2eq) added. The reaction mixture was cooled to –15°C and stirred under an atmosphere of argon. Isobutyl chloroformate (0.56mL, 4.3mmol) was added and the mixture stirred for 10mins at –15°C. A solution of diazomethane in diethyl ether (45mL, approx 40mmol) was added and the reaction allowed to warm to room temperature over 1hr, then acetic acid was added dropwise until effervescence had ceased. The reaction mixture was diluted with DCM (100mL) and washed successively with saturated aqueous sodium bicarbonate (2 x 75mL), water (75mL) and brine (75mL) and dried over sodium sulphate. The solvent was removed *in vacuo* to give crude (2S, 3S)-N-Boc-O-t-butyl-L-threonyldiazomethane (1.2g, ~100%) as a pale yellow oil. The above synthesis was repeated 9 times and the total crude product pooled (12g) and used without purification for the next stage.

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(75) Inventors/Applicants *(for US only)*: **QUIBELL, Martin** [GB/GB]; 23 Fennec Close, Cherry Hinton, Cambridge CB1 9GS (GB). **TAYLOR, Steven** [GB/GB]; 100 Holly Trees, Bar Hill, Cambridge CB3 8SG (GB).

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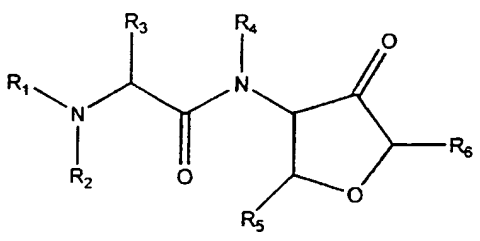
(54) Title: FURANONE DERIVATIVES AS INHIBITORS OF CATHEPSIN S



(II)

(57) Abstract: Cathepsin S is a highly active cysteine protease belonging to the papain superfamily. It is found mainly in lymph nodes, spleen, and macrophages and this limited occurrence suggests the potential involvement of this enzyme in the pathogenesis of degenerative disease. The invention relates to novel protease inhibitors, particularly inhibitors of the cysteine proteases of the papain superfamily and more particularly to Cathepsin S. The inhibitors are Furanone derivatives of Formula (II) which have a characteristic non-hydrogen substituent R5. They are selective over other members of the family and in particular show selectivity over other members of the Cathepsin family such as L and K.

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INTERNATIONAL SEARCH REPORT

Inten nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/12 C07D307/68 C07D405/12 C07D409/14 C07D405/14
C07D307/32 A61K31/4015 A61K31/365 A61K31/40 A61K31/381
A61P37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 603 873 A (MITSUBISHI CHEM IND) 29 June 1994 (1994-06-29) abstract; claims	1,13-16
Y	WO 98 50533 A (FENWICK ASHLEY EDWARD ;GRIBBLE ANDREW D (GB); SMITHKLINE BEECHAM P) 12 November 1998 (1998-11-12) cited in the application page 27 -page 58; examples	1,13-16
Y	WO 97 40066 A (MASSACHUSETTS INST TECHNOLOGY ;BRIGHAM & WOMENS HOSPITAL (US); PLO) 30 October 1997 (1997-10-30) cited in the application abstract; claims	1,13-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 00/01894

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